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The Effects of Explosive Blast as Compared to Post-Traumatic
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14. ABSTRACT The purpose of the present study is to better characterize and differentiate the effects of combat stress and explosive blast on the brain. To achieve this goal, we have been collecting extensive data on emotional health via clinical interviews and self-report measures, as well as information on brain structure and function using sophisticated magnetic resonance imaging (MRI) sequences and high density quantitative electroencephalography (EEG). We have collected clinical, EEG, and MRI data on 92 military personnel who have been deployed to Operation Iraqi Freedom or Operation Enduring Freedom. We have also established data entry and processing guidelines for clinical, EEG, and MRI data, thus ensuring that we have completed all tasks in a manner consistent with our Statement of Work for the second year of the study. The results of this study should add to clinicians' understanding of how to better diagnose and treat blast-related brain injury and post-traumatic stress symptoms.					
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Introduction

The clinical presentation of individuals with blast-related neural damage and post-traumatic psychopathology are markedly similar and thus a clear description of the direct consequences of explosive blast is complicated by the emotional and cognitive sequelae of psychological trauma. The inability to clearly demonstrate the basis of symptomatology has led to confusion for the soldier and his or her loved ones as well as difficulty prescribing effective treatments and developing interventions that return injured soldiers to adaptive functioning. In the current study, we will use sophisticated measures of neural function and structure to characterize brain injury from explosive blasts in a sample of Operation Iraqi Freedom (OIF) National Guard soldiers who returned from deployment in the fall of 2007. To fully characterize the effects of blast on the brain and differentiate them from post-traumatic stress disorder, we will contrast groups of soldiers exposed to blast with groups experiencing post-traumatic stress disorder. The study will provide a means for separating co-occurring conditions of brain injury due to explosive blast and post-traumatic psychopathology. Information that clarifies the basis of symptoms in blast-related brain injury and post-traumatic stress disorder will improve diagnostic separation of the two conditions. In summary, this investigation will improve the characterization of blast-related traumatic brain injury, describe the essential features of the condition in terms of neural function and structure to inform diagnosis, and characterize mechanisms of recovery after blast-related neural injury to allow the creation of interventions that return soldiers to maximum levels of functioning.

Body

Based on the proposed statement of work, the following milestones were projected to occur within the second year of the study:

1. Data processing pipelines designed and established

Over the second year of grant funding we have established pipelines for the processing of structural magnetic resonance imaging (MRI) data and electroencephalogram (EEG) recordings. The MRI structural data pipeline includes quality control measures that are employed shortly after data collection to ensure acceptable data quality. The EEG processing pipeline involves visual review of all EEG files gathered from subjects. We have also developed an independent components analysis (ICA) based approach to EEG artifact identification and removal that will facilitate good signal-to-noise in the EEG data. This will be of particular importance when time-frequency analyses are employed to characterize EEG abnormalities that might be associated with blast-related mild traumatic brain injury. Finally, the computational and information technology infrastructure has been fully established and now supports the analysis and management of complex neuroimaging data.

In the past year, study personnel have also set up a relational database for the study, which is a sophisticated means of linking different databases so that data pulls can be flexibly carried out and data audits can be efficiently performed. During this past year, creation of this database was a priority. Study personnel have also been trained to access data within the database in order to perform data analysis on existing data.

2. 1st and 2nd cohort data entered, processed, and stored

Data entry:

As mentioned above, during the past year, study personnel have created a relational database to store data gathered as part of this study. This database is now functional and we have established a procedure by which initial data is entered for each participant who has consented to be in our study. All participants who have been consented into the study have demographic, clinical, and biological data entered into the database. According to study procedures, all consented participants have data entered on a regular basis shortly after they enter our study. Lab personnel have essentially entered all available data to date. A majority of study personnel have been trained in data entry for the database, and processes are in place for checking the accuracy of data entry.

Data processing:

Traumatic Brain Injury (TBI) Consensus: Our research team has met regularly to create and refine a process in which raters with expertise in the field of neuropsychology and brain injury are able to score severity of brain injury in our participants (Nelson, Hoelzle, McGuire, Ferrier-Auerbach, Charlesworth, & Sponheim, 2010). We have created a rating scheme and our consensus group of doctoral level neuropsychologists and psychologists meets regularly to discuss how to categorize cases.

Mental Health Consensus: Graduate-level lab personnel under supervision by doctoral level staff have been trained to double-check clinical interview data to ensure accuracy and confirm the consensus clinical diagnosis.

Data storage:

Electronic Data: We have approval from relevant institutional review boards to store data both at the Minneapolis VAMC and at the University of Minnesota. For electronic data, we house most data to be used for data analysis in neuroimaging and EEG data sets and a relational database on servers at the University of Minnesota. Information in all data sets is only accessible by first entering a password to access the secure server, then by entering a second password to access the database. Identifiable information is housed behind the VA firewall. Within the secure VA IT infrastructure study information is stored on a drive that is accessible only to lab and VA IT personnel. All documents with identifiable participant information on this server are additionally password protected.

Hard Copies of Data: We store paper copies of data at the Minneapolis VA in locked filing cabinets within locked offices. We store identifiable information separately from clinical and biological data gathered as part of this study.

3. Preliminary data analysis

Preliminary analyses reveal that we have successfully enrolled individuals with significant exposure to explosive blasts as well as those suffering from post traumatic stress symptomatology. This permits an examination of how these aspects of contemporary battle impact brain function and structure. Initial analyses of indices of brain structure fail to reveal discernable evidence of abnormalities from exposure to explosive blast. However, complete analyses of structural data and EEG-based measures of brain function await data collection on additional subjects.

4. Telephone screen to obtain second 45 subjects

At the end of this year, our goal, as stated on our Statement of Work, was to have obtained a total of 90 participants (45 within this past year). Recruitment of potential participants into our study has been a primary focus of this study. Initially, we had hoped to recruit only participants who had taken part in a sister study and who appeared, based on their responses to this sister study, to be likely to meet inclusion criteria for our study. However, due to low base rates of PTSD, we have expanded our recruitment strategies within the past year in an effort to meet our stated goals of eventually obtaining 45 individuals in each of 4 groups: PTSD (PTSD, No Blast Exposure), Blast (Blast Exposure, No PTSD), PTSD and Blast, and Control (neither PTSD nor Blast). We have received approval from all relevant institutional review boards to use multiple strategies. Thus, in the past year, we have recruited participants in the following ways:

1. Recruiting individuals who have taken place in a sister study and who have expressed interest in being contacted for future research.

2. Coordinating with clinical teams at the Minneapolis VA in order to obtain referrals of potential participants who are likely to meet inclusion criteria for our study. This strategy has been implemented in an effort to reach more individuals with symptoms of PTSD and blast-related brain injury.
3. Contacting the OIF/OEF program at our local VA Medical Center in an effort to broaden our recruitment strategies. Through this program, we have been able to distribute flyers to recently returned service members, as well as establish relationships with clinicians at the Minneapolis VA who might be able to refer potential participants to our study.
4. Screening potential participants who have been referred by word of mouth or by other participants in our study.
5. During this quarter, we have also collaborated with another study to target individuals with combat-related PTSD to increase the number of participants with PTSD in our sample.

Our recruitment strategy involves sending letters to potential participants if they have not yet contacted us regarding study participation. We then follow up with potential participants by calling them to determine interest and eligibility for study participation. As of the end of this year (as of 3/31/10), we have sent out 306 letters to participants notifying them of our study. In addition, 30 participants have contacted us after being self-referred or referred to our study by another participant or clinical provider. Of those 336 potential participants (those contacted via letter and those who contacted us):

- Number of Participants (out of the participants who were originally sent letters without contacting us first) attempted contact via phone: 300
- Number of Participants not reached via phone (invalid number; never reached by study personnel): 100
- Number of Participants not interested in participating: 33
- Number of Participants excluded for medical history or waitlisted: 63

5. Gather clinical, EEG, and MRI data on 2nd cohort

We have continued to collect data on participants during this quarter at a rate that is consistent with our Statement of Work.

Total Number of participants who gave informed consent for, are currently taking part in, and/or completed the study: 92

Control Group: 35

Blast Group (Blast Exposure, NO PTSD): 32

PTSD Group (PTSD, No Blast Exposure): 8

Blast and PTSD Group: 17

74 participants have completed all procedures

12 participants have completed some procedures and will not be completing the rest

Since our last annual report (at which time 16 participants had been consented into our study), 76 additional participants have consented to be in our study. We have calculated the rate of participant recruitment necessary in order for us to meet our goal of obtaining

180 participants over the next two years. The rate of recruitment needed to meet our recruitment goals is well within our means.

Key Research Accomplishments

- As an overarching goal of the study, we expect that as a result of this research, both researchers and clinicians will be able to differentiate between clinical presentations of PTSD versus mild TBI. At this point, it is difficult to differentiate between the two disorders because their clinical presentations are similar. Additionally, the diagnosis of mild TBI is not without controversy. We hope that our research will clarify differences between the two disorders, and thus lead to better treatment of the disorders.
- As part of this study, we have developed a tool that we use to categorize the severity of blast and nonblast head injuries on a continuum (Nelson, Hoelzle, McGuire, Ferrier-Auerbach, Charlesworth, & Sponheim, 2010). We plan to study the psychometric properties of this tool and eventually disseminate the tool for public use.
- We have established a researcher guided system for applying independent component analysis (ICA) to electroencephalogram (EEG) data.

Reportable Outcomes

Submitted Publications

Nelson, N.W., Hoelzle, J.B., McGuire, K.A., Ferrier-Auerbach, A.G., Charlesworth, M.J., Sponheim, S.R. (2010). *Neuropsychological evaluation of blast-related concussion: Illustrating the challenges and complexities through OEF/OIF case studies*. Manuscript submitted for publication.

Sponheim, S.R., McGuire, K.A., Kang, S.S., Davenport, N.D., Aviyente, S., Bernat, E.M., & Lim, K.O. (2010). *Enhanced Measurement of Disrupted Functional Connectivity in the Brain After Blast Exposure*. Manuscript submitted for publication.

Conference and Invited Presentations

McGuire, K. A., Nelson, N. W., Hoelzle, J. B., Ferrier-Auerbach, A. G., Charlesworth, M. J., Armstrong, M., & Sponheim, S. R. (2010, June). *Persistent Postconcussive Symptoms and PTSD in OEF/OIF Military Personnel*. Presented at the annual conference of the American Academy of Clinical Neuropsychology (AACN), Chicago, IL.

Sponheim, S.R., Bernat, E.M., Kang, S.S., & Aviyente, S. (2009, September). *A new measure for characterizing deficient functional connectivity of the brain after blast injury*. Presented at the Military Health Research Forum, Kansas City, Missouri.

Sponheim, S.R. (2009, June). *Update: Differentiation of the Effects of Explosive Blast from Post-traumatic Stress of Brain Function and Structure*. Presented at Mental Health PSL Grand Rounds, Minneapolis VAMC.

Sponheim, S.R., Bernat, E.M., Kang, S.S., & Aviyente, S. (2009, May). *Enhanced Measurement of Disrupted Functional Connectivity in the Brain after Blast Injury*. Presented at the International State-of-the-Science Meeting on Non-Impact, Blast-Induced Mild Traumatic Brain Injury. Herndon, Virginia.

Sponheim, S.R. (2008, May). *New projects in blast injury and SPMI health services genomics*. Presented at Mental Health PSL Grand Rounds, Minneapolis VAMC.

Sponheim, S.R. (2008, April). *The effects of explosive blast as compared to post-traumatic stress disorder on brain function and structure*. Presented at the 4th Annual VISN 23 Mental Health Research Conference, Minneapolis, MN.

Related Projects

- Bernat, E.M. (Chair), Malone, S., Aviyente, S., Kang, S.S., & Sponheim, S.R. (2009, October). *Beyond Wavelets: Utilizing uniform time and frequency resolution to improve measurement of brain activity and functional connectivity*. Symposium conducted at the annual meeting of the Society for Psychophysiological Research. Berlin, Germany.
- Ferrier-Auerbach, A.G., Erbes, C.R., Polusny, M.A., Rath, M., & Sponheim, S.R. (2010). Predictors of emotional distress reported by soldiers in the combat zone. *Journal of Psychiatric Research*, 44, 470-476.
- Hoelzle, J. B., Nelson, N. W., McGuire, K. A., Sponheim, S. R., Ferrier-Auerbach, A. G., & Charlesworth, M. J. (2010, February). *Secondary gain context impacts neuropsychological performances among OEF/OIF veterans with histories of blast-related concussion (mTBI)*. Poster session presented at the annual conference of the International Neuropsychological Society, Acapulco, Mexico.
- Hoelzle, J. B., Nelson, N. W., McGuire, K. A., Sponheim, S. R., Ferrier-Auerbach, A. G., & Charlesworth, M. J. (2009, September). *Blast-Related Concussion (mTBI): Preliminary neuropsychological findings*. Presented at Psychiatry Grand Rounds, Minneapolis VAMC, September 4, 2009.
- Nelson, N.W., Hoelzle, J. B., McGuire, K. A., Ferrier-Auerbach, A. G., & Charlesworth, M. J., & Sponheim, S. R. (2010, June). *Predictors of neuropsychological dysfunction among veterans of Operation Iraqi Freedom (OIF)*. Poster session presented at the annual at the annual meeting of the American Academy of Clinical Neuropsychology (AACN).
- Nelson, N. W., Hoelzle, J. B., McGuire, K. A., Ferrier-Auerbach, A. G., & Charlesworth, M. J., & Sponheim, S. R. (2010, June). *The Minnesota blast exposure screening tool (MN-BEST): Introducing a systematic investigatory approach to blast exposure and concussion in Veterans of Operation Iraqi Freedom (OIF)*. Poster session presented at the annual at the annual meeting of the American Academy of Clinical Neuropsychology (AACN).
- Nelson, N. W., Hoelzle, J. B., McGuire, K. A., Sim, A. H., Goldman, D., Ferrier-Auerbach, A. G., & Charlesworth, M. J., Arbisi, P. A., & Sponheim, S. R. (2010, June). *Context matters: Examination of MMPI-2 and MMPI-2-RF validity scales among OEF/OIF veterans evaluated in forensic, clinical, and research settings*. Poster session presented at the annual at the annual meeting of the American Academy of Clinical Neuropsychology (AACN).
- Nelson, N. W., Hoelzle, J. B., McGuire, K. A., Sponheim, S. R., Ferrier-Auerbach, A. G., & Charlesworth, M. J. (2010, February). *Blast-Related Concussion (mTBI): Preliminary neuropsychological findings*. Poster session presented at the annual conference of the International Neuropsychological Society, Acapulco, Mexico.

Conclusion

The major accomplishments of the first year were to establish methods of data collection and recruitment and to begin to recruit participants into our study. This entailed obtaining permissions from relevant institutional review boards. During the second year of grant funding, we have continued to recruit participants in a manner consistent with our Statement of Work. We have collected clinical, EEG, and MRI data on these recruited participants. We have also established data entry and processing guidelines, thus ensuring that we have completed all tasks in a manner consistent with our Statement of Work for the second year of the study. We have calculated the rates of data collection necessary to complete data collection on approximately 90 participants (for a study total of 180 participants) within the next 18 months, which would give us a 6-month cushion at the end of the study. Given the remaining 18 months in which we would like to collect data, we have calculated that we will need approximately six clinical visits per month, which will entail needing to perform phone screens on at least twice that many people per month. This data collection plan is well within our means, and we are confident that this plan will allow us to reach our goal of obtaining complete data within the allotted study period.

We expect that data collected as part of this study will add to what is known about alterations in brain function and structure associated with exposure to blasts in battle. Inclusion of a group of subjects affected by post-traumatic stress symptomatology from battle will allow the differentiation of the emotional consequences of explosions from the effects of the blast-related pressure wave. Identification of brain abnormalities unique to each condition (blast-related TBI and post-traumatic stress) will help clinicians and researchers accurately assess conditions evident in soldiers exposed to explosions. Such knowledge will also inform the design of treatments that return the injured to optimal levels of functioning. The results of this study may also help military leadership and health care professionals prescribe treatments that are personalized to an individual's underlying brain pathology.

References

Nelson, N.W., Hoelzle, J.B., McGuire, K.A., Ferrier-Auerbach, A.G., Charlesworth, M.J., Sponheim, S.R. (2010). *Neuropsychological evaluation of blast-related concussion: Illustrating the challenges and complexities through OEF/OIF case studies*. Manuscript submitted for publication.

Appendices